General

Guideline Title

Cancer of the uterine cervix.

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Team. Cancer of the uterine cervix. Edmonton (Alberta): CancerControl Alberta; 2013 Apr. 16 p. (Clinical practice guideline; no. GYNE-004). [97 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Team. Cancer of the uterine cervix. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Apr. 15 p. (Clinical practice guideline; no. GYNE-004).

Recommendations

Major Recommendations

Staging of cervical cancer is based on the Fédération Internationale de Gynecologie et d'Obstétrique (FIGO). The classification system was updated in 2010. A detailed description of this staging system can be found in the Appendix of the original guideline document.

Staging

Investigations may include:

- History and clinical examination
- Cervical biopsy; an expert pathology review should be performed by a pathologist with experience in gynecologic pathology
- Blood work (complete blood count [CBC], liver function test [LFT], renal function studies)
- Imaging is optional for stage <IB1. For IB1 and higher, magnetic resonance imaging (MRI) is recommended; chest x-ray and positron emission tomography-computed tomography (PET-CT) may be performed
- Cone biopsy, as indicated

Treatment

FIGO Stage IA1

Preferred options include:

- Conization with free margins
- OR simple hysterectomy
- OR modified radical hysterectomy if there is multifocal invasion
- If there is lymphovascular space involvement, consider pelvic lymphadenectomy

FIGO Stage IA2

Preferred options include:

- Conization +/- pelvic lymphadenectomy (PLND) +/- para-aortic lymphadenectomy (PALND)
- OR simple or modified radical hysterectomy +/- pelvic lymphadenectomy +/- PALND
- OR radical trachelectomy for fertility preservation +/- pelvic lymphadenectomy +/- PALND

Special Considerations

Radical trachelectomy indications:

- Preservation of fertility
- Small adenocarcinomas can be considered at physician discretion
- No lymphovascular (LVS) invasion; limited endocervical involvement

FIGO Stage IB1

Preferred options include:

- Radical hysterectomy + pelvic lymphadenectomy +/- PALND; adjuvant post-operative radiotherapy is considered only when adverse pathological findings are found
- OR pelvic radiotherapy (RT) + brachytherapy. This is usually considered for patients who are not candidates for surgery; although less evidence is available to support the addition of chemotherapy to primary radiotherapy for this subgroup, chemoradiation is the preferred option
- OR radical trachelectomy + pelvic lymphadenectomy +/- PALND could be considered for patients wishing fertility preservation

Post-operative adjuvant therapy guidelines as described below will be applied to this subgroup.

FIGO Stage IB2

Preferred options include:

- Pelvic RT + concurrent chemotherapy (cisplatin × 5–6 cycles) followed by brachytherapy
- OR radical hysterectomy + pelvic lymphadenectomy +/- PALND

Post-operative adjuvant therapy guidelines as described below will be applied to this subgroup.

FIGO Stage IIA1

Preferred options include:

- Pelvic RT + concurrent chemotherapy (cisplatin × 5–6 cycles) followed by brachytherapy
- OR radical hysterectomy + pelvic lymphadenectomy +/- PALND *in selected circumstances*

Post-operative adjuvant therapy guidelines as described below will be applied to this subgroup.

FIGO Stage IIA2

Preferred options include:

- Pelvic RT + concurrent chemotherapy (cisplatin × 5–6 cycles) followed by brachytherapy
- OR radical hysterectomy + pelvic lymphadenectomy +/- PALND *in selected circumstances*

Post-operative adjuvant therapy guidelines as described below will be applied to this subgroup.

FIGO Stage IIB/IIIA/B/IV

Options include:

- Medically fit patients: tailored EBRT + concurrent chemotherapy (cisplatin × 5–6 cycles) followed by brachytherapy
- Medically unfit patients: palliative or radical RT can be given at the discretion of the radiation oncologist

Post-operative Adjuvant Therapy

Consider the following risk factors when deciding on appropriate treatment options:

- Histology (e.g., adenocarcinoma, adenosquamous versus squamous cell carcinoma)
- Tumour size
- Depth of stromal invasion
- Lymphovascular space invasion (LVSI)
- Nodal status
- Parametrial margin status
- Vaginal margin status

Radiation Therapy

Radiation therapy should be administered as follows:

Pelvic RT: 45–50.4 Gy in 25–28 fractions (1.8–2.0 Gy per fraction) over 5–5.5 weeks

- Intracavitary brachytherapy may include high dose rate (HDR) or pulsed dose rate (PDR) techniques.
- Boost to the parametria may be given as clinically indicated.

Note: It is recommended to maintain adequate hemoglobin during radiotherapy.

Special Clinical Scenarios

- Adjuvant hysterectomy may be considered among patients in whom intracavitary insertion is unsuccessful after the initial chemoradiation, and the patient is unable to have brachytherapy (Walji et al., 2010).
- If intracavitary brachytherapy cannot be performed, and patient is not a surgical candidate, consider a smaller pelvic boost technique (e.g., 3-dimensional [3-D] conformal or intensity modulated radiotherapy [IMRT] may be considered) (Lertsanguansinchai et al., 2004).

Chemotherapy

- Cisplatin should be administered at a dose of 40 mg/m^2 (max = 80) intravenously over 1 hour weekly for 5–6 cycles during EBRT (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008).

Recurrent/Persistent Disease

Investigations may include:

- History and clinical examination
- Blood work (CBC, LFT, renal function studies)
- Imaging: chest x-ray; CT-PET chest, abdomen and pelvis, MRI of the pelvis

Treatment options for *curable* pelvic recurrence include:

- Radical radiotherapy, with or without cisplatin, for patients previously treated with surgery
- Pelvic exenteration, for patients previously treated with upfront radical radiotherapy

Treatment for *incurable* pelvic recurrence may include palliative radiotherapy and chemotherapy.

Treatment options for extra-pelvic recurrences include:

- Clinical trial
- Palliative chemotherapy
- Palliative radiotherapy

<u>Follow-up and Surveillance</u>

The following recommendations have been modified from the Cancer Care Ontario (see the "Adaptation" field) follow-up guidelines:

- Inform patients about symptoms of recurrence.
- For the first 2 years, patients should be followed closely by a physician experienced in the surveillance of cancer patients; follow-up visits should be held every 3 to 4 months within the first 2 years.
- After the first 2 years, the patient can be discharged to the primary care physician; follow-up visits should be held annually and should include annual cytology.
- Follow-up visits should include a history (e.g., any symptoms elicited) and complete physical examination (including a speculum exam with bimanual and pelvic/rectal examination).
- There is little evidence to suggest that vaginal vault cytology more than once a year is useful.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cancer of the uterine cervix

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Pathology

Radiation Oncology

Radiology

Surgery

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide recommendations for the staging, treatment, and follow-up of cervical cancer

Target Population

Adults over the age of 18 years with cancer of the uterine cervix, including squamous, adenocarcinomas, and adenosquamous carcinomas

Interventions and Practices Considered

Evaluation

1. History and clinical examination
2. Cervical biopsy with expert pathology review
3. Cone biopsy as indicated
4. Blood work (complete blood count [CBC], liver function test [LFT], renal function studies)
5. Imaging: chest x-ray, computed tomography/positron emission tomography (CT/PET), CT or magnetic resonance imaging (MRI)

Treatment/Management

1. Conization with free margins
2. Simple hysterectomy
3. Modified radical hysterectomy
4. Pelvic lymphadenectomy
5. Para-aortic lymphadenectomy (PALND)
6. Radical trachelectomy for fertility preservation
7. Adjuvant post-operative radiotherapy
8. Pelvic radiotherapy (RT)
9. Brachytherapy
10. Chemotherapy (cisplatin)
11. External beam radiotherapy (EBRT)
12. Treatment of recurrent or persistent disease including radical radiotherapy, pelvic exenteration, palliative radiotherapy and chemotherapy
13. Follow-up and surveillance

Major Outcomes Considered

- Quality of life
- Overall survival
- Disease-free survival
- Overall response rate
- Progression-free survival

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

1. What should be considered during the staging of patients so that the appropriate primary treatment is given?
2. Does radiotherapy following surgery, versus surgery alone, increase survival rates among patients with early stage disease?
3. What are the appropriate indications for adjuvant therapy either after primary surgery or radiotherapy?
4. Is chemoradiotherapy more effective than radiotherapy alone in increasing survival? If so, what is the optimal platinum-containing chemotherapy regimen?

Search Strategy

Entries to the Medline, EMBASE, and Cochrane databases and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms included: *cervix* or *cervical* or *uterine cervix* AND *carcinoma* or *neoplasm* or *cancer*, with limits of human studies in females only. Among the studies returned by the search, those that did not report survival or toxicity outcomes and those that had fewer than 100 patients per treatment arm were excluded.

Guidelines reviewed include the following: the National Comprehensive Cancer Network (NCCN) guidelines (2010), the European Society for Medical Oncology (ESMO) guidelines (2009), the BC Cancer Agency (BCCA) guidelines (2006), and Cancer Care Ontario (CCO) Program in Evidence-Based Care guidelines (2004–2009), and the Tom Baker Cancer Centre (2008). The guideline was originally developed in 2009 and then updated in 2011, 2012, and again in 2013. The literature was reviewed prior to each update, using the search strategy described above. The 2012 and 2013 reviews included a total of 21 studies and 2 studies, respectively.

Number of Source Documents

The 2012 and 2013 reviews included a total of 21 studies and 2 studies, respectively.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those

meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

An effort was made to either adapt or adopt the most appropriate guidelines from other sources so that work wasn't duplicated. An evidence based perspective was used to draft proposals. Where evidence was weak a guideline was developed using pragmatic consensus within the group. Following a review of the evidence by the Alberta Provincial Gynecologic Oncology Team, no major changes were made to the recommendations and the guideline was reaffirmed.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of

Provincial Tumour Programs.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008 Dec 10;26(35):5802-12. PubMed

Lertsanguansinchai P, Lertbutsayanukul C, Shotelersuk K, Khorprasert C, Rojpornpradit P, Chottetanaprasith T, Srisuthep A, Suriyapee S, Jumpangern C, Tresukosol D, Charoonsantikul C. Phase III randomized trial comparing LDR and HDR brachytherapy in treatment of cervical carcinoma. Int J Radiat Oncol Biol Phys. 2004 Aug 1;59(5):1424-31. PubMed

Walji N, Chue AL, Yap C, Rogers LJ, El-Modir A, Chan KK, Singh K, Fernando IN. Is there a role for adjuvant hysterectomy after suboptimal concurrent chemoradiation in cervical carcinoma. Clin Oncol (R Coll Radiol). 2010 Mar;22(2):140-6. PubMed

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management and treatment of patients with cancer of the uterine cervix

Potential Harms

- Adverse events and toxicity associated with therapy
- There is significant toxicity associated with the combination of cisplatin with topotecan.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Team. Cancer of the uterine cervix. Edmonton (Alberta): CancerControl Alberta; 2013 Apr. 16 p. (Clinical practice guideline; no. GYNE-004). [97 references]

Adaptation

Recommendations on follow-up and surveillance were modified from the following source: Elit L, Fyles A, Fung-Kee-Fung M, Oliver T, and the Gynecology Cancer Disease Site Group. Follow-up for Women after Treatment for Cervical Cancer: Guideline Recommendations: A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO). Evidence-Based Series #4-16: Report Date: April 13, 2009.

Date Released

2012 Apr (revised 2013 Apr)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

Guideline Committee

Alberta Provincial Gynecologic Oncology Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Team. Cancer of the uterine cervix. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Apr. 15 p. (Clinical practice guideline; no. GYNE-004).

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 10, 2012. The information was verified by the guideline developer on January 23, 2013. This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on May 22, 2014.

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